X1 is Ser or Gly, and

X2 is Ser or Pro.

14. (Amended) A isolated peptide of claim 13, comprising the motif X0-X1-Ser-Cit-His-X2 (SEQ ID NO: 8), wherein X0 is Asp.

15. (Amended) A isolated peptide of claim 14, comprising the motif X0-X1-Ser-Cit-His-X2-X3 (SEQ ID NO: 9), wherein X3 is Gly or Arg.

REMARKS

Election/Restriction Requirement

Applicants thank the Examiner for vacating the restriction requirement. Thus, claims 1, 3, 5-7, and 9-15 are currently before the Examiner for consideration.

Compliance with 37 CFR 1.821(d)

Claims 13-15 have been amended to recite sequence identifiers. Attached is a paper copy of the Sequence Listing, a Computer Readable Format of Sequence Listing on diskette, and a Statement accompanying the Sequence Listing.

Status of the Claims

Claims 1, 3, 5-7, and 9-15 are pending in the instant application. Claims 1, 5-7, 9-10, and 12-15 have been amended to more clearly claim the subject matter of the invention.

Claims 1, 5, and 13-15 have been amended to insert "isolated." Support can be found on page 6, line 29.

Claims 1 has been amended to delete "tripeptide." Support can be found in the original claim.

Claims 5, 9, 10, 13-15 have been amended to recite "peptide" instead of "antigen" and 6, 7, and 12 have been amended to recite "a peptide/antibody complex" instead of "an antigen/antibody complex." Support can be found in claim 1.

Claim 6 has been amended to clearly provide the steps of the claimed invention. Support can be found on page 7, line 30 to page 8, line 7.

Claims 7 and 12 have been amended to replace "as well as suitable" with "and." Support can be found in the original claim.

Claims 13-15 have been amended to insert sequence identifiers.

Rejection of Claim 6 Under 35 U.S.C. § 112, First and Second Paragraphs

Claim 6 has been rejected under § 112, first and second paragraphs, as being incomplete and not enabling for omitting the essential steps. Claim 6 has been amended to more clearly claim the subject invention. Claim 6 as it now stands includes all the essential steps. Thus the rejection has become moot.

Objection of the Claims

Claim 6 has been objected to for missing the word "at" in line 3. Claim 6 has been amended to insert "at" in line 3. Thus, the objection has become moot.

Claims 13-15 have been objected for failing to recite the sequence identifiers. Claims 13-15 have been amended to include the sequence identifiers. Thus, the objection has become moot.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 5, 9, 10, and 13 are rejected under § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Claim 1 has been amended to recite "the motif Ser-Cit-His".

Claims 5, 6, 7, 9, 10, and 12 have been amended to replace "antigen" with peptide.

Claim 6 has been amended to delete "by any suitable means".

Claim 7 has been amended to delete "as well as suitable".

Claim 12 has been amended to delete "as well as".

Accordingly, the rejection has become moot.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1, 3, 5-7, and 9-15 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification.

Applicants respectfully point out that peptides comprising the motif Ser-Cit-His are described on page 5 of the specification and in the Examples. SEQ ID NO: 3, 5, and 6 represent the native filaggrin peptides from which the citrullinated peptides described in the instant application were obtained. Examples 1-3 of the present application describe steps for obtaining citrullinated peptides comprising Ser-Cit-His and for testing the peptides against autoantibodies from RA patients.

Specifically, Example 2 describes the citrullination, of S-47-S (SEQ ID NO: 3) and S-35-R (SEQ ID NO: 4) by *in vitro* deamination under the action of P.A.D. S-47-S comprises the Ser-Arg-His motif, while S-35-R (SEQ ID NO: 4) does not contain the motif. However, both peptides comprise several Arg residues. Upon completion of deamination of these peptides, deaminated S-47-S comprises the Ser-Cit-His motif while S-35-R does not. As shown in Example 2, only citrullinated 2-47-S peptide is recognized by a serum from a patient suffering from RA, whereas citrullinated S-35-R is not recognized by the serum.

Specifically, Example 3 describes the preparation of citrullinated E-12-H (SEQ ID NO: 5) and E-12-D (SEQ ID NO: 6) peptides by solid phase synthesis with direct incorporation of a citrulline residue in place of an arginine. Native peptides E-12-H and E-12-D both comprise the Ser-Arg-His motif. The native E-12-H comprises a single arginine residue. The native E-12-D comprises 3 arginine residues, only one of them is in the Ser-Arg-His motif. Thus, only one Arg is replaced by a citrulline during solid phase synthesis. As shown in Example 2, citrullinated E-12-H and E-12-D both comprise the Ser-Cit-His motif and not other citrulline residue. Both peptides are recognized by anti-filaggrin antibodies (AFAs). The corresponding non-citrullinated peptides are not recognized by AFAs.

As discussed in the specification and specifically shown in the Examples, when the Arg residue in the Ser-Arg-His motif is citrullinated peptide, the citrullinated peptide is recognized by serum from patient suffering from RA or by AFAs. It is also pointed out that citrullination of S-35-R which comprises several Arg but no Ser-Arg-His motif did not yield a peptide that reacts with the AFAs in the serum of RA patients. Thus, the Ser-Arg-His is essential for AFA recognition.

Accordingly, Applicants have described in the specification several examples of citrullinated peptides comprising Ser-Cit-His that are recognized by AFAs and serum from RA patients. Accordingly, Applicants have provided adequate written description of the claimed peptides. Thus, Applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 101

Claims 1, 5, 9, 10, and 13-15 are rejected under § 101, as being directed to non-statutory subject matter. Claims 1, 5, and 13-15 have been amended to insert "isolated" before "peptide". Thus, the rejection has become moot.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3, 5-7, and 9-15 are rejected under § 103(a) as being unpatentable over Schellekens *et al.*

Not in claims.

Schellekens *et al.* report that synthetic peptides containing citrulline react with autoantibodies present in the sera of RA patients. However, the reference does not teach or suggest that the amino acid residues flanking the citrulline are also important for the immunoreactivity.. Given the teachings of Schellekens *et al.*, one of ordinary skill in the art would have concluded that any citrulline containing peptide was able to react with AFAs present in the serum from RA patients. One of ordinary skill in the art would not have been motivated to obtain peptides comprising the Ser-Cit-His motif as claimed in the present invention. It would not have been obvious from the teachings of Schelleckens *et al.* that the peptide must possess the Ser-Cit-His motif for AFA recognition.

The Office Action also cited the reference of Serre *et al.* (FR 96/10651). Serre *et al.* identify filaggrin as an antigen but do not suggest that citrullinated epitopes play a role in RA autoantibody recognition. In fact, Serre *et al.* discloses reactivity of profilaggrin which is not citrullinated. Thus, Serre *et al.* do not cure the deficiencies of Schellekens *et al.*,

Accordingly, Applicants respectfully request withdrawal of this rejection.

Conclusion

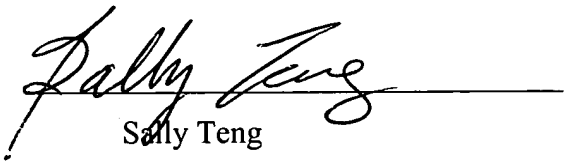
In view of the amendments and accompanying remarks, Applicants respectfully request reconsideration and timely allowance of the pending claims. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact Applicants' undersigned representative to expedite prosecution.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

Dated: May 30, 2003

By: 

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Version of Amended Claims with Markings to Show Changes Made

IN THE CLAIMS:

1. (Amended) [~~A~~] An isolated peptide comprising an epitope recognized by anti-filaggrin autoantibodies present in serum from rheumatoid arthritis patients, wherein said epitope comprises the [~~tripeptide~~] motif Ser-Cit-His in which Cit represents a citrulline residue.

5. (Amended) An isolated antigenic composition for diagnosing the presence of rheumatoid arthritis-specific autoantibodies in a biological sample, containing at least one [antigen] peptide according to Claim 1.

6. (Amended) A method for detecting rheumatoid arthritis-specific autoantibodies in a biological sample comprising:

contacting said biological sample with at least one [~~antigen~~] peptide according to Claim 1 under conditions which allow the formation of [~~an antigen~~] a peptide/antibody complex with any rheumatoid arthritis-specific autoantibodies possibly present in the biological sample;

removing [~~the rest of said biological sample after said antigen/antibody~~] the unbound peptide from the peptide/antibody complex [~~is formed~~]; and

detecting[~~, by any suitable means, any antigen/antibody~~] the presence of the complex, [~~formed~~] whereby the presence or absence of rheumatoid arthritis-specific autoantibodies in said biological sample is determined.

7. (Amended) A kit for detecting rheumatoid arthritis-specific autoantibodies in a biological sample comprising at least one [~~antigen~~] peptide according to Claim 1, [~~as well as suitable~~] and buffers and reagents for constituting a reaction medium which allows the formation of [~~an antigen~~] a peptide/antibody complex, and/or means for detecting said [~~antigen~~] peptide/antibody complex.

9. (Amended) The antigenic composition of Claim 5 wherein the at least one [~~antigen~~] peptide is labeled.

10. (Amended) The antigenic composition of Claim 5 wherein the at least one [~~antigen~~] peptide is conjugated to a carrier molecule.

12. (Amended) A kit for detecting rheumatoid arthritis-specific autoantibodies in a biological sample, comprising at least one [~~antigen~~] peptide according to Claim 1, [as well as] and means for detecting the [~~antigen~~] peptide/antibody complex.

13. (Amended) [~~A~~] An isolated peptide of claim 1, comprising the motif X1-Ser-Cit-His-X2 (SEQ ID NO: 7), wherein

X1 is Ser or Gly, and

X2 is Ser or Pro.

14. (Amended) [~~A~~] An isolated peptide of claim 13, comprising the motif X0-X1-Ser-Cit-His-X2 (SEQ ID NO: 8), wherein X0 is Asp.

15. (Amended) [~~A~~] An isolated peptide of claim 14, comprising the motif X0-X1-Ser-Cit-His-X2-X3 (SEQ ID NO: 9), wherein X3 is Gly or Arg.